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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/376,395	08/18/1999	LEAF HUANG	226272002201	6461

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	20

DATE MAILED: 08/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/376,395	Applicant(s) HUANG ET AL.	
	Examiner Richard Schnizer	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-86,88-95,97-101,103-123,125-131 and 133-155* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-86,88-95,97-101,103-123,125-131 and 133-155* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/10/02 has been entered.

An amendment and an IDS were received and entered as Paper Nos. 18 and 19, respectively, on 6/10/02. Claims 46-76, 96, and 132 were canceled, and claims 137-155 were added as requested. Claims 77-86, 88-95, 97-101, 103-123, 125-131, and 133-155 are pending and under consideration in this Office Action.

The invention as originally filed was drawn to drug compositions and methods of making and using them. In response to a restriction requirement, applicant elected in Paper No. 10 group III drawn to therapeutic compositions comprising nucleic acids and methods of making and using them. Applicant also elected asialoglycoprotein as the species of targeting ligand to be examined. Examination remains limited to these elected inventions. The species of asialoglycoprotein is considered to read on all pending claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 77-86, 88-95, 97-101, 103-123, 125-131, and 133-155 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12, 14-21, 23-28, 30-33, 35-44 and 46 of U.S. Patent No. 6,008,202 ('202). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons. Instant claim 77 is drawn to a composition comprising a nucleic acid/lipid/polycationic polypeptide salt complex and a targeting factor. Claim 8 of '202 is drawn to a composition **comprising** a nucleic acid/lipid/polycationic polypeptide salt complex. At column 12, lines 58-63 of '202, it is disclosed that the composition may also comprise a targeting ligand, so instant claim 77 is obvious in view of claim 8 of '202. Similarly, instant claims 98 and 104 differ from claims 31 and 40 of '202 only in that the instant claims recite a targeting factor, so the instant claims are obvious over the patented claims. Each of the limitations of the

instant claims is disclosed in the specification or claims of '202, and is therefore embraced by the indicated claims. For example, Claim 2 of '202 teaches the charge required by instant claim 78, and the limitations of claims 79-83 are found at column 3, lines 6-8 and 57-61; and column 13, lines 30-62. Claim 5 of 202' teaches a polycationic polypeptide that is a sulfate salt, as required by instant claims 84 and 85. Claims 7 and 9-13 of '202 teach protamine sulfate, a nucleic acid encoding E1A, DC-Chol, a polypeptide between 20 and 100 amino acids in length, and a neutral phospholipid, as required by instant claims 86 and 88-92. Claims 16-18 and 20 of 202' correspond to instant claims 93-95 and 97. Claims 25-28, 30, 34, 37, and 38 of 202' correspond to instant claims 98-101, and 103-106. The limitations of instant claims 107-115 are found at column 12, lines 65-67; and column 16, lines 15-24, combined with claims 1 and 37, and the method of claim 116 is obvious in view of claims 2 and 37 of '202. Because the instant application is a continuation of the application resulting in the '202 patent, all of the instant limitations will find support in '202. While the specification of an issued patent generally cannot be used as prior art to support a double patenting rejection, the courts have found that the portion of a patent disclosure which supports the patent claim may be considered when determining double patenting. "[T]his use of the disclosure is not in contrainvention of the cases forbidding its use as prior art, nor is it applying a patent as a reference under 35 USC 103, since only the disclosure of the invention claimed in the patent may be considered." See *In re Vogel* 422 F.2d 438, 441-42, 164 USPQ 619 (CCPA 1970). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the

issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. See MPEP 804 (II). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 77-86, 88-95, 97-101, 103-123, 125-131, and 133-155 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising the E1A gene, at least one lipid species, and a polycationic polypeptide salt, wherein the composition has a net positive charge, and for a method of administering the composition to an animal wherein the composition is delivered directly to the site of tumor cells intended to receive the E1A gene, as taught in US Patent 6,008,202, does not reasonably provide enablement for a composition, or a method of administering the composition, wherein the composition comprises a net neutral or net negative charge, or wherein the composition has a net positive charge but does not comprise a gene encoding E1A, or for any claimed composition comprising an asialoglycoprotein targeting ligand, or for methods of systemic administration. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

The claimed invention encompasses compositions comprising a nucleic acid, at least one lipid species, and a polycationic polypeptide salt, and methods of making and using the compositions. Claims 77-86, 88-95, 97-101, 103-112, 137-146, 154 and 155 require a targeting ligand. In Paper No. 10, Applicant elected asialoglycoprotein as the targeting ligand under consideration. Claims 77, 78, 80-82, 84-86 88-95, 97-101, 103-120, and 122-155 allow the complex to have a positive, neutral, or negative charge. Claims 113-123, 125-131, 133-136, and 147-153 recite various routes of administration.

The elected invention requires that the nucleic acid is intended to be used as a drug. The specification defines the term "drug" at page 4, lines 15-18 as a molecular entity administered to an individual for the purpose of therapy. For this reason, a "drug" as defined by the specification must be therapeutic if it is to be used as intended. Therefore, in order to enable the invention commensurate in scope with the claims, the specification must teach how to use the claimed compositions as drugs, i.e. therapeutically.

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all

current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). Because the existing delivery and expression techniques cannot be used to predictably treat diseases, it is necessary for the specification to provide guidance to the skilled artisan as to how to overcome the factors which hamper gene delivery and expression such that a therapeutic result is achieved. It is noted that because the claims encompass gene therapy generally, the scope which must be enabled is very broad and includes the treatment of any disease with any gene.

The specification teaches a working example of gene therapy in which the survival of mice injected intraperitoneally with tumor cells is prolonged by subsequent intraperitoneal administration of compositions comprising cationic polypeptides, lipids, and a nucleic acid encoding an E1A polypeptide. The specification fails to disclose the net charge of these

compositions. See example 18, pages 53 and 54. US Patent 6,008,202, issued to Applicant, discloses the identical working example, and recites claims drawn to drug/lipid/polycationic polypeptide compositions comprising a net positive charge. See claim 2 of '202'. This patent is presumed to be valid, thus compositions comprising the net positive charge are presumed to be enabled. However, as one of skill in the art appreciates that most cells carry a net negative surface charge, delivery compositions of net negative or neutral charge would reasonably be expected to interact differently with target cells than would compositions of net positive charge. Such compositions are embraced by all claims except claims 78, 79, 82, 83, 116, 117, 120, and 121. Clearly, the interaction of the composition with target cells is of critical importance to the function of the invention. In the absence of a targeting ligand, one of skill in the art would reasonably expect that the affinity of the net neutral or negative compositions for a given cell would be less than that of a positively charged composition. Because the specification does not disclose a working example of the compositions in gene therapy, and due to the unpredictability associated with the delivery of gene therapeutics as set forth by Orkin, Verma, and Anderson above, it is not clear that negative or neutral compositions would provide the same benefit as the positively charged versions. Furthermore, the claims broadly encompass compositions and methods for the purpose of gene therapy in general. This scope encompasses the treatment of any disease, and with the exception of claims 88 and 125 which recite the E1A gene, any gene may be used for treatment. However, the E1A gene is the only example of a therapeutic gene disclosed in the specification, and the specification. teaches how to treat only one disease with

this gene. In view of the broad scope encompassed by the claims, the disclosure of only a single therapeutic gene, and its use to treat only one disease, one of skill in the art would have to perform undue experimentation in order to practice the invention commensurate in scope with the claims.

Consideration of Example 18 also raises the issues of systemic versus local delivery, and the use of targeting ligands. This example employs direct injection at the site of the tumor, whereas the claims encompass systemic intravenous delivery. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al. reviews the types of vectors available for *in vivo* gene therapy, including retroviral, adenoviral, liposomal, and molecular conjugates, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998) reviews ligand-targeted receptor mediated vectors, and indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but which are currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion

section). Verma et al. (1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each. Verma clearly indicates that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Crystal also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Thus the general state of the art for targeted delivery of nucleic acids is immature in the context of therapeutic applications, necessitating direct administration of nucleic acids to the intended target site, rather than systemic administration.

The instant specification contemplates receptor-mediated targeting of transfection complexes. However, Perales et al (PNAS 91:4086-4090 (1994a)) teach that receptor mediated gene targeting is unpredictable. These authors emphasize the need to "better characterize, the individual components of the DNA/ligand complex and to understand the nature of their assembly into a dependable vehicle for gene delivery." For example, the authors address the importance of the size of ligand-bound delivery complexes, noting that most endocytic receptors discriminate against ligands of a determined size range *in vivo*. See page 4086, paragraph bridging columns 1 and 2; and column 2, first full paragraph. With specific respect to the asialoglycoprotein receptor, the targeting ligand elected by Applicants, Schlepper-Schafer et al (Exp. Cell Res. (1986) teach that ligands of greater than 7.8 nm in diameter are not taken up via this receptor. See abstract. In this context, it is noted that the instant specification fails to teach an

example of the claimed compositions which is less than 35 nm in diameter, or to specifically contemplate a particle of the size which can be taken up by asialoglycoprotein receptor-mediated endocytosis. See Fig. 20. In fact, the specification teaches that the optimum size for coated pit internalization is 200 nm, thereby teaching away from a particle size which can be internalized by the asialoglycoprotein receptor. See page 11, lines 1 and 2.

Perales et al (Eur. J. Biochem. 226:255-266 (1994b) teach that, for receptor-mediated targeting to be useful in gene therapy, "it is critical that both the chemical properties and physical interactions of the reagents involved in the design of the DNA delivery vehicle be rigorously characterized." See abstract. In order to obtain particles of a size which can be internalized by asialoglycoprotein receptor-mediated endocytosis, it appears to be necessary to form particles comprising only a single DNA molecule complexed with the targeting ligand and polycation. See page 257, column 2, first and second full paragraphs. The formation of such complexes requires extremely low concentrations of DNA, the slow addition of a polycation comprising the targeting ligand, followed by titration with NaCl. Perales does not teach the use of lipids in combination with these complexes, as is required by the instant claims. The instant specification does not contemplate the formation of the claimed complexes by addition of DNA to polycations in the absence of lipids as taught by Perales (1994a) (see *e.g.* page 17, lines 17-25), nor does the specification teach how to predict the effect of lipids on the particle size. On the contrary, Fig. 20 of the application shows that 50 different variations of the concentrations of the individual components of the complexes failed to produce particles of average size of less than 150 nm, and

there is no clear trend which would allow one of skill in the art to predict how such a complex might be formed using the methods of the instant invention. Reduction of the lipid:DNA ratio resulted in a decrease in particle size to 35 nm, (see Table 4 on page 38), but again, the lack of any trend in these results would not allow one of skill in the art to predict how to form a complex of the appropriate size taught by Schlepper-Schafer. The specification also fails to address the possible effects of adding shielding components such as polyethylene glycol to the complex as required by claims 95, 97, 131, 133, 137, 138, 142, 143, 154, and 155.

In view of the broad scope encompassed by the claims, the disclosure of only a single therapeutic gene, its use to treat only one disease, the general state of the art of gene therapy, the state of the art of targeted vector delivery in general, the state of the art of targeting using asialoglycoprotein, the lack of working examples of the use of asialoglycoprotein, or guidance as to how to use asialoglycoprotein with particles of the size preferred in the specification, one of skill in the art would have to perform undue experimentation in order to practice the invention commensurate in scope with the claims.

Response to Arguments

Applicant's response filed 6/10/02 has been fully considered but is not persuasive.

Applicant asserts that the amendments and remarks filed 6/10/02 represent a sincere effort to overcome the rejections and address all issues that were raised in the outstanding Office Action. Applicant has not specifically addressed why any of the amendments overcomes any portion of the rejection, and the rejection is maintained for the reasons set forth above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JAMES KETTER
PRIMARY EXAMINER